UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,583	06/25/2003	Kai Y. Xu	A9422	5808

23373 7590 10/31/2007

SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,583	XU, KAI Y.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *8-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment to the claims filed August 17, 2007 is acknowledged.

   Claims 1-7 have been amended.

   Claims 1-47 are pending.

   Claims 8-47 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to a non-elected invention.

   Claims 1-7 are under examination as they read on an antibody which recognizes the amino acid sequence comprising SEQ ID NO: 1.

2. The previous rejections of record can be found in the Office Action mailed May 17, 2007.

   This Office Action is in response to applicant's amendment to the claims filed August 17, 2007.

   The previous rejection under 35 U.S.C. § 101 has been withdrawn in view of applicant's amendments to the claims.

   The previous rejection under 35 U.S.C. § 112, 2nd paragraph has been withdrawn in view of applicant's amendments to the claims.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph has been withdrawn in view of applicant's amendments to the claims.

3. As requested by applicant, the Examiner confirms that applicant claims the benefit of priority of USSN 60/391,514, filed June 25, 2002.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

   A person shall be entitled to a patent unless –

   > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
   >
   > (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international

application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1 and 4-7 stand rejected under 35 U.S.C. 102(e) as anticipated by Rosen et al., (US 20030054421) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44, essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

Applicant argues that the antibodies of Rosen do not anticipate the instant claims because neither Rosen nor the evidentiary references establish that the antibodies of Rosen necessarily bind SEQ ID NO: 1. Applicant also argues that it is known in the art that substitution of even one amino acid can alter or inhibit the binding activity of an antibody or enzyme citing scientific articles published by Rudikoff et al. and Witkowski et al. in support of this argument. Applicant further argues that the amino acid differences between the prior art antigen of Rosen – TEEEP**Q**ND**N** – and SEQ ID NO: 1 – RSATEEEPPNDD – are qualitatively different from the amino acid difference between the cross-reactive polypeptides of Bost et al. – LEHLLL – and – LERILL –, and therefore Bost does not provide sufficient evidence to support that the antibody of Rosen raised against TEEEPQNDN would necessarily bind to SEQ ID NO: 1 – RSATEEEPPNDD.

Applicant's argument has been considered and has been found convincing for claims 2 and 3 in that, upon reconsideration, given the teachings of Rosen as evidenced by Bost and Bendayan, one of ordinary skill in the art would come to the conclusion that the antibodies of Rosen may or may not bind the RSATEEEPPND amino acid sequence rather than that the antibodies of Rosen would necessarily bind the RSATEEEPPND amino acid sequence.

However, Applicant's argument has not been found convincing for claims 1 and 4-7, essentially for the reasons of record as put forth in the Office Action mailed

With respect to Applicant's argument that it is known in the art that substitution of even one amino acid can alter or inhibit the binding activity of an antibody or enzyme citing scientific articles published by Rudikoff et al. and Witkowski et al., it does not appear the applicant has provided either abstracts or full length versions of these publications so it is difficult to fully evaluate applicant's argument.

However, in so far as Rudikoff shows that a single amino acid change in an antibody can alter its binding to an antigen or Witkowski shows that a single amino acid change in an enzyme can alter its enzymatic activity, this does not appear to be germane to the instant rejection in that the issue at hand is the cross-reactivity of antibodies, e.g., the antibodies of Rosen, against a particular polypeptide, e.g., human NaK ATPase, for a polypeptide with homology to said polypeptide, e.g., Rat NaK ATPase.

With respect to applicant's other arguments, they are not found convincing because as stated in the prior Office Action of May 17, 2007, Rosen not only teaches antibodies against TEEEPQNDN, but Rosen also teaches antibodies against SEQ ID NO: 745 as a whole, which is 94% identical across residues 1-707 of the Rat NaK ATPase sequence obtained from Genbank accession number AAA416781 wherein the Rat Genbank sequence comprises SEQ ID NO: 1 of the instant application. Rosen further teaches antibodies against various other antigenic epitopes of SEQ ID NO: 745 which are 100% identical to other regions of Rat NaK ATPase, such as 41-GVGRDKYE-48 (see, in particular, page 75, row 12 and the alignment mailed with previous Office Action of May 17, 2007).

Given the extensive homology (94%) across the full length SEQ ID NO: 745 and amino acid residues 1-707 of the Rat NaK ATPase, as well as Rosen's teachings about antigenic epitopes of SEQ ID NO: 745 which are 100% identical to Rat NaK ATPase, the antibodies of Rosen necessarily recognize the amino acid sequence comprising RSATEEEPPNDD, i.e., Rat NaK ATPase, as evidenced by Bost and Bendayan for the reasons of record put forth in the Office Action of May 17, 2007.

Thus, claims 1 and 4-7 stand anticipated by Rosen as evidenced by Bost and Bendayan.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind a polypeptide comprising SEQ ID NO: 1. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

6. **Claims 1, 4 and 7 stand rejected under 35 U.S.C. 102(b)** as anticipated by Ball et al. (Biochim Biophys Acta. 1987 Nov 5;916(1):100-11) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886), and as further newly evidenced by Harlow et al. (Antibodies, Cold Spring Harbor Press, pp. 72-78 (1988)), essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

Applicant argues that Ball does not anticipate the claimed invention for the same reason that Rosen does not do so. Namely, that neither Ball nor the evidentiary references establish that the antibodies of Ball necessarily bind SEQ ID NO: 1. Furthermore, applicant argues that it is known in the art that substitution of even one amino acid can alter or inhibit the binding activity of an antibody or enzyme citing scientific articles published by Rudikoff et al. and Witkowski et al. in support of this argument. Applicant further argues that the amino acid differences between the prior art antigen of Ball – **EA**ATEEEP**Q**ND**N** – and SEQ ID NO: 1 – RSATEEEPPNDD – are qualitatively different from the amino acid difference between the cross-reactive polypeptides of Bost et al. – LEHLLL – and – LERILL –, and therefore Bost does not provide sufficient evidence to support that the antibody of Ball raised against EAATEEEPQNDN would necessarily bind to SEQ ID NO: 1 – RSATEEEPPNDD.

Applicant's argument has been considered, but has not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

With respect to Applicant's argument that it is known in the art that substitution of even one amino acid can alter or inhibit the binding activity of an antibody or enzyme citing scientific articles published by Rudikoff et al. and Witkowski et al., please see Section 5 above.

With respect to applicant's other arguments, it is the Examiner's position that the polyclonal antibodies of Ball bind to a sequence of amino acids with 6 centrally located residues 100% identical to centrally located residues of SEQ ID NO: 1. As is well known to one of ordinary skill in the art, polyclonal antibodies bind multiple epitopes throughout the immunizing antigen, and 6 amino acids were well known by one of ordinary skill in the art to be sufficient for generating an antibody response as evidenced by Harlow et al., see in particular, page 76, 2nd paragraph.

Therefore, the polyclonal antibodies of Ball will inherently bind SEQ ID NO: 1 as evidenced by Bost and Bendayan for the reasons of record put forth in the Office Action of May 17, 2007 and as further evidenced by Harlow et al.

Accordingly, the antibodies of Ball anticipates the instant claims.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind a polypeptide comprising SEQ ID NO: 1. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

7. **Claims 1-3, 5 and 7 stand rejected under 35 U.S.C. 102(b)** as anticipated by Arystarkhova et al., (J Biol Chem. 1992 Jul 5;267(19):13694-701) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586), Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44, essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

Applicant argues that Arystarkhova does not anticipate the instant claims because "even a change of a single amino acid may produce a significant change in the binding affinity of an antibody," and for the same reasons that Rosen does not anticipate the instant claims.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

Applicant's argument is not found convincing because in discussing the results of their efforts to "map the antigenic determinant within the α subunit of porcine NaK ATPase" (see page 13698, left column 1st paragraph and Figure 7) which is "evidently composed primarily of contiguous amino acids" using fine-specificity analysis Arystarkhova states, "[o]n either side of this cluster [referring to residues 114-EEEP-117], substitution in rat α1 of serine for Ala^{112} or proline for Gln^{119} reduces affinity slightly relative to that for pig α1." (see column bridging paragraph on page 13700).

Thus, Arystarkhova teaches that the Vg4 antibody binds an epitope composed primarily of contiguous amino acids QAATEEEPQNDNL of pig α1 NaK ATPase, wherein the "crucial" EEEP residues are conserved between rat α1 and porcine α1 NaK ATPase AND Arystarkhova further teaches that Vg4 does indeed bind rat α1 NaK ATPase with an affinity slightly lower than its affinity for porcine α1 NaK ATPase.

Thus, in contrast to applicant's argument, the Vg4 antibody of Arystarkhova does indeed recognize the amino acid sequence comprising RSATEEEPPNDD, i.e., Rat α1 NaK ATPase, wherein Arystarkhova teaches that residues EEEP, which are conserved between the rat α1 and pig α1 NaK ATPase, are crucial for Vg4 binding.

Accordingly, the teachings of Arystarkhova, as evidenced by Bost, Bendayan and the instant specification, anticipate the instant claims.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind a polypeptide comprising SEQ ID NO: 1. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. **Claims 1-3 and 5-7 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Arystarkhova et al., (J Biol Chem. 1992 Jul 5;267(19):13694-701) in view of Rosen et al. (US 20030054421), Schwinger et al. (Circulation. 1999 Apr 27;99(16):2105-12), Mohraz et al. (J Biol Chem. 1994 Jan 28;269(4):2929-36), Bost et al. (Immunol. Invest. 1988; 17:577-586), Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44, essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

Applicant argues, "[t]o begin with, the Office Action states that 'it would have been obvious to one of ordinary skill in the art to prepare humanized Vg4 antibodies for the purpose of monitoring heart function in vivo.' *Office Action of 17May 2007,* page 12. Applicant, however, is not claiming humanized Vg4 antibodies in any of the pending claims. Rather, Applicant is claiming a humanized antibody that binds to SEQ ID NO: 1. Thus, the Office Action's conclusion is irrelevant to the claimed invention." Applicant further argues that a case for *prima facie* obviousness has not been made because "neither Arystarkhova, Rosen, Ball, nor the other cited references teach or suggest all the claim limitations of the invention, either explicitly or inherently. In particular, these references do not expressly or inherently teach an antibody which is known to recognize the amino acids sequence listed in the claims."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed May 17, 2007.

As stated above, Arystarkhova teaches that the Vg4 antibody binds an amino acid sequence comprising RSATEEEPPNDD, i.e., Rat α1 NaK ATPase, and teaches that residues EEEP, which are conserved between the rat α1 and pig α1 NaK ATPase, are crucial for Vg4 binding. Thus, the Vg4 antibody of Arystarkhova is an antibody which recognizes an amino acid sequence comprising RSATEEEPPNDD, and a humanized Vg4 antibody will have the same epitope specificity. Thus, in contrast to applicant's argument the Office Action's conclusion is entirely relevant to the claimed invention because the instant claims read on humanized Vg4 antibody, even if the instant claims do not explicitly recite "humanized Vg4 antibodies" as pointed out by applicant. Moreover, a prima facie case of obviousness has been made because the cited references do teach the claimed limitations.

Therefore, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
October 29, 2007

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

10/29/07